

REMARKS

Entry of this amendment after final action is requested under 37 C.F.R. 1.116 to place the claims in better condition for allowance. Upon entry of this amendment, claims 1-6, 9-10 and 17-23 will be currently pending. Claims 7 and 8 are cancelled herein, claims 11-16 were previously withdrawn and claims 17-23 have been newly introduced herein. Amendment and/or cancellation of claims herein is made without abandonment of the original subject matter; Applicants' reserve the right to pursue claims of the original or similar scope in a duly filed continuing application.

Claim 1 has been amended to include limitations of claims 7 and 8. In addition, support for the recitation of "carried by the vector" in amended claim 1 is found on page 4, line 20, and page 7, line 12, of the application as originally filed. Support for the recitation of "capable of inducing an antibody response" is found at page 7, lines 12-13, and support for "capable of inducing a T cell response" is disclosed in the headline in the middle of page 5 of the specification. Support for "the T cell response is biased towards an inflammatory T-helper response" is found on page 7, last paragraph of the specification.

Claims 2-6 and 9-10 have been amended to replace "according to" with "of" as requested by the Examiner. Misspellings such as "listeriolysin" in claim 9 have been corrected.

Support for new claim 17 can be found in the specification as originally filed on page 7, last paragraph. Support for new claim 18 is found at page 7, third and fourth paragraphs. Support for new claim 19 is found at page 4, lines 13 and 18. Support for claim 20 is found at page 4, line 20, and page 8, last line. Support for claim 21 (induction of antibody response after a single immunization) is found on page 7, lines 13-14 and in Figures 3A and 3B. Support for claim 22 (T cell response induced after a single immunization) is found at page 6, first line in the second paragraph for CD8 and page 6, last paragraph, fourth line from the bottom, for CD4, as well as in Figures 1C, 1F, 2C and 2F. Support for claim 23 is found in claim 9.

Thus, all claim amendments herein find basis in the original specification and no new matter has been introduced.

OUTSTANDING REJECTIONS

Various objections to the abstract, specification and claims were maintained for reasons set forth in the Office Action mailed March 29, 2002.

The rejections of claims 1-10 under 35 U.S.C. § 112, second paragraph for asserted indefiniteness were maintained.

The rejections of claims 1-10 under 35 U.S.C. § 112, first paragraph as assertedly lacking enablement for the full scope of the claims were maintained.

The rejections of claims 1-4, 7, 8 and 10 under 35 U.S.C. § 102(e) over Curtiss, III *et al.*, U.S. patent No. 5,656,488 (hereafter "Curtiss, III"), were maintained.

The rejections of claims 1, 2, 7, 8 and 10 under 35 U.S.C. § 102(b) over Srinivasan, *et al.*, *Biol. Reproduct.* 53:462-471 (1995) (hereafter "Srinivasan") were maintained.

The rejections of claims 1-10 under 35 U.S.C. § 103(a) over Curtiss III in view of Rock, U.S. Patent No. 5,869,057 (hereafter "Rock"), Vogelstein *et al.*, U.S. Patent No. 6,054,570 (hereafter "Vogelstein") or Chada *et al.*, U.S. Patent No. 5,736,388 (hereafter "Chada"), were maintained.

RESPONSE

1. Objections to the abstract, specification and claims

The objection to the abstract was previously addressed by the presentation of a new abstract in Applicants' amendment mailed August 29, 2002. The new abstract is one paragraph and less than 150 words and is believed to comply with MPEP 608.01(b).

The objection to the specification as being informal in format was previously addressed by Applicants' amendment mailed August 29, 2002, which inserted appropriate section headings and a new Summary of the Invention section.

The objection to the specification as incorporating material by reference to a foreign application is addressed herein by Applicants' amendment of the specification to remove the incorporation by reference.

The objection to the specification for use of the abbreviation "CMV" is addressed herein by Applicants' amendment of the specification to insert the corresponding full name "cytomegalovirus". It is well known in the art that CMV is a standard abbreviation for cytomegalovirus and so antecedent basis for this term in the specification is not required. (See, for example, page 171 of Renato Dulbecco, "Virology", 2nd Edition (1988), and the subject index on page 1303 of Fields *et al.*, "Fundamental Virology", 3rd Edition (1996), attached hereto as Exhibits A and B respectively). In fact, the Examiner has used the term "CMV" as an

abbreviation for "cytomegalovirus" as well (see page 14, 4th full paragraph, of the August 13, 2003 action).

Although the Examiner objected to the specification for not italicizing names of bacterial species, upon review of the entire specification (including the specific lines on page 5 referred to by the Examiner), Applicants have not identified any bacterial species names that are not italicized.

The objections to the claims have been addressed in Applicants' amendments of the claims. Inasmuch as all of the outstanding objections have been addressed herein or in previous amendments, Applicants believe that these objections may properly be withdrawn.

2. The rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 and 7 for asserted indefiniteness of the term "fragment" may properly be withdrawn in view of Applicants' amendments of the claims to clarify the characteristics of the gene fragment as encoding a polypeptide, a protein and/or a protective antigen that is capable of inducing an antibody and T cell response as recited in amended claim 1.

The rejection of claim 9 for asserted indefiniteness of the term "variant" may properly be withdrawn for the same reason, since claim 9 depends from claim 1 which recites the characteristics of the variant.

The rejection of claim 8 for asserted indefiniteness of the term "protective" is mooted by cancellation of this claim.

For these reasons, Applicants believe that all rejections under 35 U.S.C. § 112, second paragraph may properly be withdrawn as not applicable to the currently pending amended claims.

3. The rejections under 35 U.S.C. § 112, first paragraph

The rejection of all claims 1-10 as assertedly lacking enablement for the full scope of the claim may properly be withdrawn because it would not require undue experimentation to construct gene fragments encoding fragments of polypeptides that elicit the desired immune response recited in claim 1. In fact, the specification shows that the attenuated *Salmonella* vaccine elicited an immune response for at least three completely different polypeptides, β -galactosidase, listeriolysin and ActA.

The Examiner's reliance on the specification's example of the ActA gene fragment encoding amino acids 31-613 as evidence of unpredictability is misplaced. The specification

shows that, in fact, the gene fragment generated both cellular and antibody immune responses, although these responses were not sufficient to rescue mice challenged with lethal doses of *Listeria*. The cellular immune response is demonstrated in Figs. 2D-2F described at page 16, lines 9-14 of the specification and the antibody immune response is demonstrated in Figs. 3A-3B described at page 16, lines 17-23 of the specification). Thus, while the specification reported that actA was non-protective against a lethal bacterial infection, the specification showed that actA did induce an immune response.

It would require no more than routine effort to prepare fragments and test them for desired activity following the guidance of the specification. In view of the guidance provided in the specification, including three working examples, the high level of skill in the art, and the well established knowledge in the art that fragments of proteins can retain antigenic properties of the whole protein, it would not require undue experimentation to produce additional vaccines having the properties recited in claim 1. According to *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), even a large quantity of experimentation is not considered "undue" provided it is only routine experimentation.

4. The rejections under 35 U.S.C. § 102(e)

Curtiss, III does not anticipate Applicants' claimed invention because Curtiss, III does not disclose or suggest that the vector carried by the avirulent microbe includes a gene sequence that encodes a polypeptide, a protein and/or a protective antigen which is capable of inducing an antibody response and a T cell response biased towards an inflammatory T cell helper response, as recited in claim 1. On the contrary, Curtiss, III focuses on the antibody (B cell) response and merely discloses that genes encoding gamete-specific antigens are useful for the production of monoclonal and polyclonal antibodies (column 49, lines 43-46). In column 42, line 34 and lines 51-59 the patent only refers to a test for IgG/sIgA responses, which are only B cell responses. Similarly, column 42, line 41-59 merely discloses that a humoral and secretory immune response was tested.

The goal of Curtiss, III is to induce an antibody response, including secretory antibody, to gamete-specific antigens in order to provide an anti-fertility vaccine. Although column 5, lines 60-61 and column 6, lines 26-29 mention a cellular (T cell) response as part of general definitions of the terms "antigen" and "immune response," the Curtis, III patent makes clear at column 6, lines 34-65 that its disclosure is restricted to the antibody (B cell) response. In particular, lines 45-49 state that "in this application the phrase ["immune response"] is restricted

to the anatomical features and mechanisms by which a multi-cellular organism produces antibodies against an antigenic material . . ."

For these reasons, Curtiss, III does not disclose or suggest all features of claim 1 as amended and, therefore, Curtiss, III does not anticipate claim 1 or claims dependent thereon.

5. The rejections under 35 U.S.C. § 102(e)

Srinivasan does not anticipate Applicants' claimed invention because the reference does not disclose or suggest that the vector carried by the avirulent microbe includes a gene sequence that encodes a polypeptide, a protein and/or a protective antigen which is capable of inducing an antibody response and a T cell response biased towards an inflammatory T cell helper response, as recited in claim 1. This reference, like Curtiss III, also focuses on the secretory antibody response to immunization with gamete-specific antigens. Although Srinivasan mentions a B cell and T cell response in the sentence bridging pages 462-463 and at page 469, left column, it does not disclose or suggest an attenuated *Salmonella* strain comprising a vector that provides a T cell response biased towards an inflammatory T cell helper response.

For these reasons, Srinivasan does not disclose or suggest all features of claim 1 as amended and, therefore, Srinivasan does not anticipate claim 1 or claims dependent thereon.

6. The rejections under 35 U.S.C. § 103

There is not a proper suggestion to combine the references cited by the Examiner, Curtiss, III, Rock, Vogelstein and Chada. Moreover, even if the references are improperly combined, the combination does not successfully teach production of Applicants' claimed invention.

The disclosure of Curtiss, III is discussed above. There is no suggestion and no incentive to combine Curtiss, III with Rock because the two references are focused on solving different problems. Curtiss, III relates to vaccines that produce an antibody response, preferably a secretory antibody response, while Rock teaches using recombinant vaccines to break self-tolerance by fusing a microbial gene product with a self protein. Although Rock generally describes the role of T cells and T-cell help in the immune response and does refer to *Salmonella* as one type of strain that has been used for oral immunization, Rock does not disclose an attenuated *Salmonella* comprising a vector including a gene sequence that encodes a polypeptide, a protein and/or a protective antigen which is capable of inducing an antibody response and a T cell response biased towards an inflammatory T cell helper response, as recited in claim 1.

Vogelstein teaches the selective expression of desired genes in cells expressing oncogenes, and does not mention an attenuated *Salmonella* vaccine for inducing an immune response. Chada merely teaches bacterial phage-mediated gene transfer systems capable of transfecting eukaryotic cells and does not mention an attenuated *Salmonella* vaccine for inducing an immune response. Therefore there is no specific suggestion to combine Curtiss, III with Vogelstein or Chada, and even if combined the references do not lead the skilled person to the invention claimed by independent claim 1.

For these reasons, the references are not properly combined and even if combined do not successfully teach production of an attenuated *Salmonella* vaccine with all the characteristics recited in claim 1. Therefore, the references do not render obvious claim 1 or claims dependent thereon.

CONCLUSION

For the foregoing reasons, each of claims 1-6, 9, 10 and 17-23 is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

Dated: November 13, 2003

Respectfully submitted,

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9 8 7 6 5 4 3

- enus, 53
 pathway of activation of, 330
 effects of, 330-331
 pathway of activation of, 330
 nplex virus protein interaction with,
 rus-infected cells by, 331
 proteins in regulation of, 1183
 receptors, HIV attachment and
 nalization and, 875
 it regulatory proteins, poxvirus,
 itary DNAs, animal viruses in
 overy of, 8
 itation, 122-124
 l activity of recombinant DNA
 es of viral genomes assessed with,
 -105
 :quences used in, 124
 ses, 708
 r resolution, in poxvirus DNA
 ication, 1178
 transition, N to H antigen
 sformation and, 511
 infections, adenovirus
 troenteritis, 979
 mean hemorrhagic fever virus, 649
 nt of, coding strategies of, 655
 : of, 650, 651
 a, as entry site in viral infection, 167
 itis, adenoviruses causing, 979
 s genus (insect parvovirus group C),
 52, 1018
 n strain, of vaccinia virus, genome
 1167-1168
 ce recombination, mapping
 tations and, 120
 id)-envelope link (CEL), HIV, 849
 otors, HIV, 878-879
 ins. *See also* Capsid proteins
 1-853
 cleavage in production of, 851, 852
 e and, 182-183
 s B virus, 1201
 i, 695, 696
 uses (Coronaviridae), 31-33, 54,
 1-559
 pathogens, 32-33
 ly of, 552
 tent of, 546-548
 eristics of, 24, 31-32
 cation of, 541-542
 hic effects of, 552-553
 ve-interfering RNA and, 554
 : associations of, 542
 :s of, 553-554
 e of, structure and organization of,
 15
 . of, 545-546
 coprotein of, 551
 nge of, 542
 pathogens, 32. *See also* Human
 onavirus
 n of, 545-546
 coprotein of, 551
 on of, 553
 sphoprotein of, 551-552
 nonstructural proteins of, 552
 penetration by, 546-548
 persistent infection caused by, 552-553
 proteins of, processing and intracellular
 transport of, 551-552
 receptors for, 175, 546-548
 replication of, 546-553
 RNA replication and, 550-551
 RNA transcription and, 548-550
 RNA recombinations and, 553-554
 S glycoprotein of, 551
 serogroups of, 541, 542
 transcription in, 548-550
 translation in
 of genomic RNA, 548
 of viral proteins, 551
 virion of, structure of, 542-545
 virion release by, 552
 Corticosteroids, for prion diseases, 1282
 Corticoviridae, 51
 Corticovirus genus, 51
 COS cells, for transient expression, 126
 Cotransfection, with selectable markers,
 125-126
 Cottontail rabbit papillomavirus (CRPV), 952
 discovery of, 947
 genomic organization of, 954
 Cowpea mosaic virus, 390
 genome organization and expression of, 390,
 392
 virion structure of, 390, 391
 Cowpox virus, 1165
 cytokine antiviral actions inhibited by, 359
 Cocksackieviruses
 electrostatic nature of attachment of, 497
 type A
 cell tropism of, 498
 receptors for, 499
 families of, 498
 type B, receptors for, 499
 families of, 498
 nature of, 499
 Cp promoter, BZLF1 interaction with, 1138
 CPE. *See* Cytopathic effects
 CPMV. *See* Cowpea mosaic virus
 CPV. *See* Canine parvovirus
 CQI. *See* Calchaqui
 CR1 protein, in herpes simplex virus
 attachment, 1053
 CR2 protein (CD21), as virus receptor, 175
 for Epstein-Barr virus, 1116-1117
 latent infection in B-lymphocytes and,
 1118
 Creutzfeldt-Jakob disease, 1246, 1247
 familial, 1246, 1247, 1279
 codon 129 homozygosity and, 1281
 PrP mutations in, 1280
 genetic mutations in, 1280
 iatrogenic, 1247, 1276, 1278
 codon 129 affecting susceptibility to, 1281
 incidence of, 1246
 sporadic, 1246, 1247
 treatment of, 1282
 Crimean-Congo hemorrhagic fever virus, 649
 S segment of, coding strategies of, 655
 structure of, 650, 651
 Crk oncogene, 275, 276
 crmA gene, cytokine antiviral actions inhibited
 by, 359
 cRNA (template RNA), influenza virus, 605
 Cro protein, in cell commitment after λ phage
 infection, 464-465
 Crop plants, virus/viroid infection of, 368-369.
See also Plant viruses
 Cross-protection, in control of plant virus
 diseases, 370
 CRPV. *See* Cottontail rabbit papillomavirus
 Cryparin, in virus induction of hypovirulence,
 438
 Cryphonectria parasitica
 reovirus of, 438
 replicons of, 430, 446
 viruses affecting virulence of, 426-427,
 437-438
 Cryptic infections, parvoviruses causing, 1026
 Cryptoviruses, 377
 Crystallization of viruses, x-ray diffraction
 studies and, 62
 cs mutations. *See* Cold-sensitive mutations
 CSF. *See* Cerebrospinal fluid; Cytostatic factor
 CSF-1. *See* Colony-stimulating factor-1
 CSFs. *See* Colony-stimulating factors
 c-src. *See* Src oncogene
 CTL. *See* Cytotoxic T lymphocytes
 CTV. *See* Citrus tristeza virus
 Cucumber mosaic virus, 394
 Cucumovirus genus, 54
 Cutter incident, 189
 Cypovirus genus (cytoplasmic polyhedrosis
 viruses), 38-39, 52, 403
 Cystoviridae, 52
 Cystovirus genus, 52
 Cytokine synthesis inhibitor factor. *See*
 Interleukin 10
 Cytokines, 341-365
 classification of by function, 343
 in cytotoxic T lymphocyte activity, 327
 general features of, 341-342
 in immune response, 328-329
 induction of synthesis of, 347-349
 by reoviruses, 720-720
 interference with in viral persistence, 216
 receptors for, 349-352
 reovirus induction of, 720-720
 signal transduction by, 349-352
 types of, 342-346
 viral infection affected by, 185, 356-357
 therapeutic applications and, 359-360
 viral replication affected by, 352-356
 viral strategies for counteraction of actions
 of, 357-359
 viruses activating, 349
 Cytolytic effect, restriction of, persistence and,
 210-212
 Cytomegaloviruses (CMV), 45-46, 51
 cytokines induced by, 349
 as helper viruses
 functions of, 1027-1028
 inhibition of, 1035
 lymphocytes and monocytes infected by, 333
 murine (*Muromegalovirus* genus), 45-46, 51
 persistence of, 208
 receptors for, 175, 176
 Cytopathic effects (CPE), 240-241. *See also*
 Cytopathogenicity
 of bunyaviruses, 667
 of coronaviruses, 552-553
 of picornaviruses, 504-505

Virology

Second Edition

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susceptibility in seronegative adults or immunologically crippled children after exposure, as a basis for early prophylaxis with immune globulin.

EPIDEMIOLOGY AND CONTROL

Varicella virus is usually transmitted in respiratory secretions, producing a highly communicable disease with high clinical attack rate. Epidemics are common among children, especially in the winter and spring. Second attacks of chickenpox apparently do not occur. Herpes zoster, in contrast, is of low incidence, is not seasonal, is recurrent, and is predominantly confined to persons over 20 years of age. As has been pointed out, a case of herpes zoster may initiate an outbreak of chickenpox, and contact with chickenpox is said to provoke attacks of shingles in partially immune persons.

An attenuated viral vaccine has been developed and undergone intensive study in immunocompromised children, particularly those with leukemia receiving chemotherapy, as well in healthy, nonimmune young children. Mild rashes and fever follow immunization in as many as 35% to 40% of children undergoing therapy, and shingles may also subsequently appear. In leukemic children receiving maintenance chemotherapy, treatment is usually suspended from 1 week before to 1 week after immunization. Serum Abs appeared in approximately 90% of these children, the attack rate after exposure was reduced from about 90% to 20%, and all cases were extremely mild.

In view of the seriousness of varicella in adults, however, one might question the wisdom of attempts to prevent infection in healthy children unless the preventive procedure can offer as lasting protection as the natural disease. As in measles (see Measles, Prevention and Control, Chap. 57), chickenpox can be prevented or modified by administering high-Ab-titer IgG to contacts within 72 hours of exposure. Prophylaxis is of particular importance for susceptible adults and for children with impaired immunity. Adenine arabinoside (vidarabine) and acyclovir (see Chap. 49) have been used with apparent success to treat disseminated disease in the seriously ill (particularly in immunologically suppressed patients) as well as in some normal adults, but additional control studies are necessary.

Cytomegalovirus (Salivary Gland Virus) Group

Salivary gland virus disease of newborns is a severe, often fatal illness, usually affecting the salivary glands, brain, kidneys, liver, and lungs. M. G. Smith, in 1956, isolated the causative agent. The term *cytomegalovirus* (CMV) was applied to the group because of the large size of the infected cells and their huge intranuclear inclusion

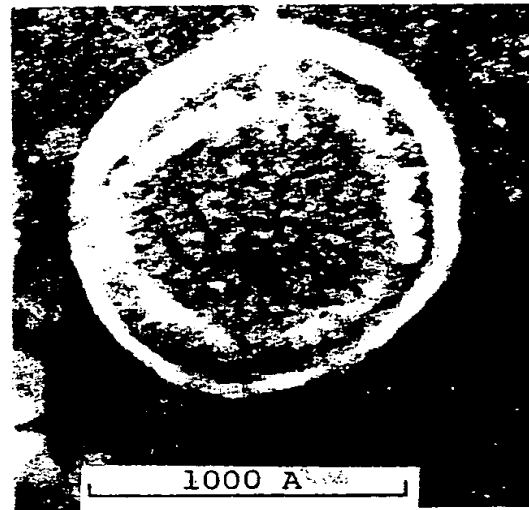


Figure 53-10. Enveloped full particle of human cytomegalovirus. (Original magnification $\times 405,000$; Wright HT Jr et al: *Virology* 23:419, 1964)

bodies. Assignment to the herpesvirus family was based on the morphology of the viral particle (Fig. 53-10), the chemical composition of the virion (see Characteristics of Members of the Herpesvirus Family), and the characteristics of the intranuclear inclusion body present in infected cells (Figs. 53-11 and 53-12).

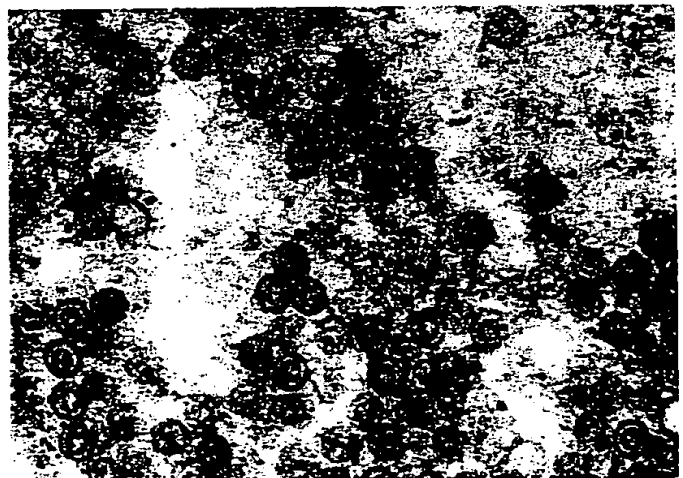


Figure 53-11. Electron micrograph of a portion of an intranuclear inclusion in a cell infected with human cytomegalovirus. The inclusion is made up of viral particles in various stages of development. Particles are composed of a central core about 40 nm in diameter, surrounded by a pale zone and, externally, by a thin membranous shell. Only a few particles have a dark central core, indicating the presence of nucleic acid. (Original magnification $\times 40,000$; Becker P et al: *Exp Mol Pathol* 4:11, 1965)